Paper 14

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte MAXIMILIAN GRASSBERGER, JOSEF G. MEINGASSNER, ANTON STUTZ and PETER STUTZ

Appeal 2001-0919[1]
Application 08/471,146[2]

Before: WINTERS and WILLIAM F. SMITH, Administrative Patent Judges, and McKELVEY, Senior Administrative Patent Judge.

McKELVEY, Senior Administrative Patent Judge.

Decision on appeal under 35 U.S.C. § 134

The appeal is from a decision of a primary examiner rejecting claims 13-26. Since filing the appeal, applicants have cancelled claims 13-18. We (1) dismiss as to cancelled claims 13-18, (2) vacate the examiner's rejection of claims 19-26 and (3) enter new grounds of rejection of claims 19-26 in place of the examiner's rejection.

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[1] The application on appeal was received at the board on 8 March 2001.

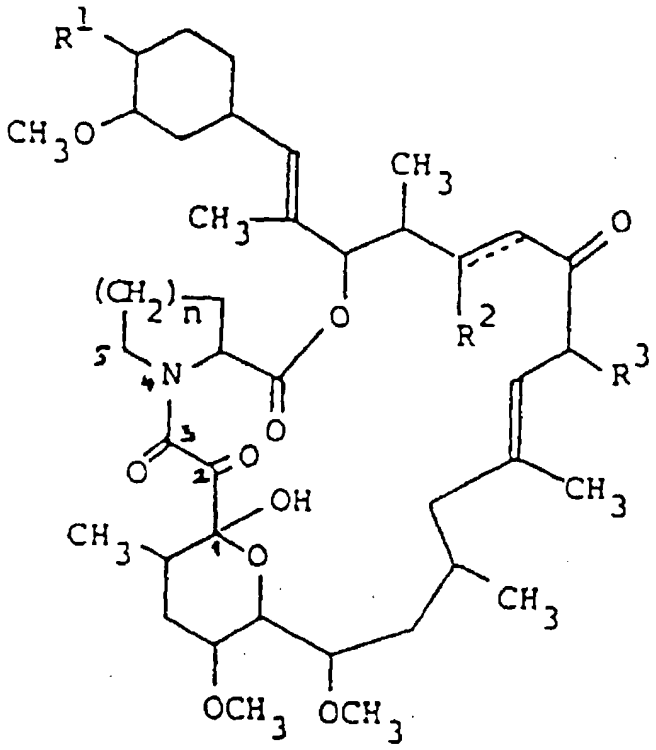
[2] Application for patent filed 6 June 1995. According to applicants, the application on appeal is a continuation of application 08/291,101, filed 15 August 1994, which is said to be a division of application 07/982,925, filed 30 November 1992 (now U.S. Patent 5,366,971), which is said to be a continuation of application 07/608,430, filed 2 November 1990, which is said to be a continuation of application 07/268,114, filed 7 November 1988. Applicants also claim priority under 35 U.S.C. § 119 of Austrian application A2952/87, filed 9 November 1987 and German application p 37 42 805.5, filed 17 December 1987. The real party in interest, as of the time the Appeal Brief was filed on 22 April 1997, was Novartis AG.

A. Findings of fact

The record supports the following findings by at least a preponderance of the evidence.[3]

The invention[4]

1. According to the specification (page 1), the invention relates to "a new use" of compounds having the formula I:



I

[3] To the extent these findings of fact discuss legal issues, they may be treated as conclusions of law.

[4] In the event of further prosecution, applicants should correct the spelling of "sodim" (sic-sodium) (specification, page 13, line 17) and "correspnds" (sic-corresponds) (page 16, line 9).

2. Further according to the specification, the compounds of formula I, methods for making the compounds and a description of their immunosuppressant and antimicrobial activity appears in European Patent Application 0 184 162 A2 (hereafter **EPA**), published 6 November 1986 (specification, page 2, lines 16-18).[5]

3. One compound described by EPA is a compound identified as Compound A or FK 506 (specification, page 16, line 1. Applicants tell us (specification, page 16, lines 2-15) that (emphasis and material in [brackets] added):

> Compound A (FK 506) is a product isolated from nature. It has a definite stereochemical configuration. However, even though it is disclosed in *** [EPA] with extensive characterization data, the formula given on [EPA] page 32 *** for FK 506 does not indicate any stereochemical configuration. There is further no indication on the precise configuration of any compound specifically disclosed in *** [EPA]. Since there are many asymmetry centers [,] the formula on [EPA] page 32 thus <u>covers many potential compounds</u>, but only one of them correspods [sic-corresponds] to FK 506. The exact configuration for FK 506 has been published subsequently, e.g., in [1] H. Tanaka et al., <u>J. Am. Chem. Soc. 109</u> (1987) 5031-5033, [2] T. Kino et al., <u>J. Antibiotics 40</u> (1987) 1249-1255 and [3] T. Taga et al., <u>Acta Cryst. C43</u> (1987) 751-753, and appears to be as follows [formula Ia]:

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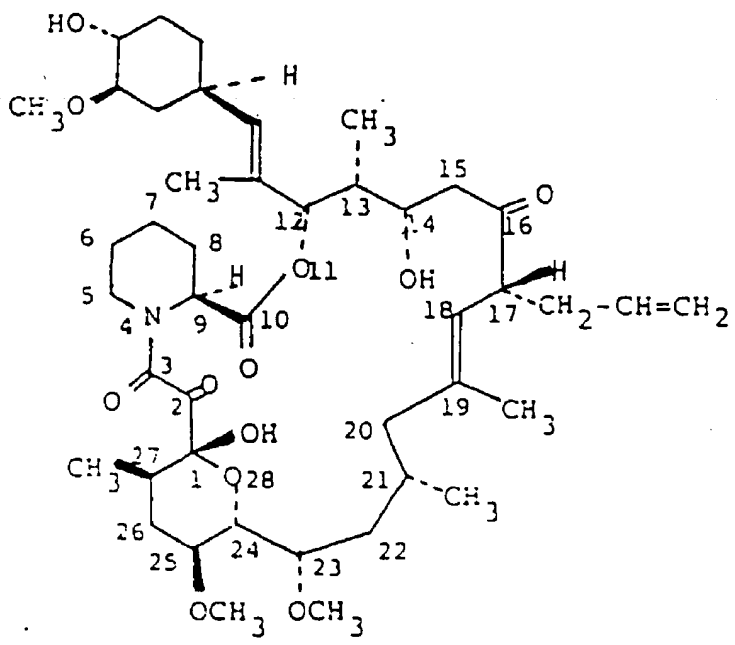
[5] EPA is prior art vis-a-vis applicant under 35 U.S.C.§ 102(b) having been published on 6 November 1986 more than one year prior to the earliest possible filing date to which applicant might be entitled, i.e., 9 November 1987.



Ia

4. Based on the foregoing statement in the specification, we understand applicants to be saying that Compound A (FK 506) described in EPA inherently has stereochemical configuration formula Ia.

5. Applicants claim to have discovered that the compounds of formula I can be used (specification, page 17, lines 1-10) (emphasis added):

> in free form or in pharmaceutically acceptable salt form in the topical treatment of inflammatory and hyperproliferative skin diseases and of cutaneous manifestations of immunologically-mediated illness, such as *** Lupus erythematosus ***.

6. With respect to a prior art compound cyclosporin A, applicants make the following observation (specification, page 2, lines 22 to page 3, line 2):

It is known and has been repeatedly published in the literature that cyclosporin A (Sandimmun®), a highly active immunosuppressant, has practically no activity upon topical administration in e.g. psoriasis (Lancet [1987] p.806; J. Invest. Dermatol. 90 [1988] 251). In animal testing for contact allergies in mice and guinea pigs cyclosporin A is only active upon topical administration of compositions containing at least 0.1%, and in the pig cyclosporin A is inactive in compositions with up to 5% cyclosporin A.

7. In the Appeal Brief (page 6), applicants reassert the proposition that "the cyclosporin art teaches that such compounds [, i.e., cyclosporins,] are generally not effective when administered in conventional topical forms."

8. On the other hand, applicants say that they have "found that surprisingly, the compounds of formula I have an excellent topical activity" (specification, page 3, lines 3-4).

9. We understand applicants to be telling us that notwithstanding the known low, or minimal, activity upon topical administration of cyclosporin A, "surprisingly" the compounds of formula I nevertheless have activity upon topical administration.

10. The specification reports various experiments with compounds falling within the scope of formula I (Compounds A through E), all of which have a stereochemical configuration similar to that of formula Ia (Finding 3). Compound A is the same compound as the compound of formula Ia.

11. Each of Compounds A through E has a formula where "n" is 2 (specification, pages 14 and 15) and none has a formula wherein "n" is 1.

12. The "especially preferred" compound for use in topical administration is Compound A (specification, page 17, lines 11-14).

13. The compound can be administered in the form of a lotion, gel or cream containing 1-3% concentration of the active compound (specification, page 17, lines 15-21).

14. The compound can be used in the lotion, gel or cream in "in free form or in pharmaceutically acceptable salt form, together with a pharmaceutically acceptable carrier or diluent" (specification, page 17, lines 22-26).

The examiner's rejection

15. The examiner rejected claims 19-26 as being unpatentable under 35 U.S.C. § 103(a) over EPA (Examiner's Answer, page 3).

16. The examiner's rejection is difficult to understand.

17. Notwithstanding a § 103 rejection has been made, the examiner failed to make an explicit finding with respect to any difference between (1) the subject matter of claim 19 and (2) EPA.

18. Additionally, the examiner cites no evidence to support his findings that (a) lotions can be a suspension,

(b) applicants' gel is usually in the form of a solid or semisolid and (c) cream is usually in the form of an emulsion.[6]

EPA

19. EPA describes compounds having formula I (page 3).

20. EPA also describes applicants' Compound A, which is also the compound of formula Ia (page 32, lines 20-30; see also applicants' specification, page 14, lines 1-7).

21. According to EPA, the compounds of formula I have "antimicrobial activity" (specification, page 2, line 17 and page 66, line 35).

22. The antimicrobial activity of the compounds of EPA formula I are described in Test 2 (pages 70-71), wherein it is said that FR-900506 (applicants' Compound A) has an antimicrobial effect at (1) a minimum inhibitory concentration (MIC) of 0.025 μg/ml against Aspergillus fumigatus IFO 5840 and (2) an MIC of 0.05 μg/ml against Fusarium oxysporum IFO 5942.

23. Further according to EPA (page 76, line 10 to page 77, line 7) (emphasis added):

> The pharmaceutical composition of this invention can be used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid form, which contains

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[6] See In re Lee, ___ F.3d ____, 61 USPQ2d 1430 (Fed. Cir. 2002) (board decision denying patent must be founded on necessary findings and must provide an administrative record showing the evidence which the findings are based; the board must assure that the requisite findings are made, based on evidence of record; when the board asserts subject matter to be general knowledge to negate patentability, that knowledge must be articulated and placed on the record). What the Federal Circuit rightfully expects from the board, the board expects from the examiner.

the tricyclo compounds (I)[7] of the present invention, as an active ingredient, in admixture with an organic or inorganic carrier or excipient suitable for external, enteral or parenteral applications. The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions, and any other form suitable for use. The carriers which can be used are water, glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea and other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form, and in addition auxiliary, stabilizing, thickening and coloring agents and perfumes may be used. The active object compound is included in the pharmaceutical composition in an amount sufficient to produce the desired effect upon the process or condition of diseases.

For applying this composition to [a] human, it is preferable to apply it by parenteral or enteral administration. While the dosage of therapeutically effective amount of the tricyclo compounds (I) varies from and also depends upon the age and condition of each individual patient to be treated, a daily dose of about 0.01-1000 mg, preferably 0.1-500 mg and more preferably 0.5-100 mg, of the active ingredient is generally given for treating diseases, and an average single dose of about 0.5 mg, 1 mg, 5 mg, 10 mg, 50 mg, 100 mg, 250 mg and 500 mg is generally administered.

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[7] The compounds of formula I of EPA and of formulas I and Ia of applicants are referred to as "tricyclo compounds" because they are "azatricyclo" compounds.

24. Other findings, as necessary, appear in the "Discussion" portion of our opinion.

B. Discussion

1. The examiner's rejection

As our findings make clear, the examiner's answer does not provide a suitable evidentiary basis upon which effective administrative review of the rejection may take place. Accordingly, we vacate the examiner's rejection and replace it with a new ground of rejection pursuant to 37 CFR § 1.196(b).

2. New ground of rejection under § 103

Claims 19-26 are rejected under 35 U.S.C. § 103(a) as being unpatentable over (1) EPA, (2) Johnson, U.S. Patent 4,411,893 and (3) Showalter, U.S. Patent 4,556,654.

EPA describes applicants' Compound A (which EPA also designates as Compound A or FK 506 or FK-900506) and reveals that Compound A has antimicrobial activity. EPA Compound A is included within the formula of claims 19. Because applicants tell us that Compound A has the stereochemical configuration of the formula of applicants' claim 23, EPA Compound A also falls within the scope of 23. Compound A has (1) an R^1 and an R^2 which are hydroxyl (—OH); (2) an R^3 which is allyl; (3) an "n" which is 2 and (4) a single (as opposed to double) bond between carbons 14 and 15. Accordingly, EPA Compound A is included within the scope of the compounds mentioned in claims 20-22.

The difference between the subject matter of claims 19-26 and EPA is that EPA does not explicitly describe a semisolid which is a lotion, gel or cream.

EPA describes Compound A as having antimicrobial activity and says that Compound A may be used as "emulsions" or "suspensions" in "semisolid" form (page 76).

EPA suggests the use of EPA Compound A as an antimicrobial agent to be applied with a "carrier" "external[ly]", i.e., topically. The prior art is well aware of how antimicrobial agents are applied topically using lotions, gels and creams.[8] For example, Johnson, U.S. Patent 4,411,893, issued 25 October 1983, teaches the use of compositions for use on skin in the form of a lotion, gel or cream (e.g., col. 3, line 56 through col. 4, line 24). Likewise describing the use of lotions, gels or creams to apply pharmaceutical compositions to skin is Showalter, U.S. Patent 4,556,645, issued 3 December 1985 (col. 16, lines 41-47; col. 40, lines 33-68):

> Topical preparations including dusting powders, creams, lotions, gels, and sprays. These various topical preparations may be formulated by well known procedures. See for example Remington's Pharmaceutical Sciences, Chapter 43, 14th ed. 1970, Mack Publishing Co., Easton, Pennsylvania 18042, USA.

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[8] Additionally, we take official notice of the fact that pharmaceutical compositions to be applied topically have been sold in the United States many years prior to applicants' earliest date in semisolid form, e.g., the pharmaceutical product sold under the trademark "NEOSPORIN".

Manifestly, the prior art establishes that a person having ordinary skill in the art wishing to apply the EPA antimicrobial compounds externally to skin would have known to do so by using, inter alia, lotions, gels or creams.

According to applicants, EPA does not "motivate" one skilled in the art to prepare lotions, gels or creams for use in topically treating patients. We disagree. EPA explicitly teaches that its compounds are antimicrobial agents. Nothing in EPA's description of Test 2 (pages 70-71) indicates that the EPA compounds must be administered internally. On the contrary, EPA explicitly teaches that its compounds may be applied externally to patients. The prior art is well aware of how antimicrobial compounds are administered topically in lotions, gels and creams. The prior art, as a whole, contains the necessary incentive, motivation, teaching, suggestion or reason to make applicants' claimed lotions, gels and creams.[9]

Applicants argue that EPA would only encourage one skilled in the art to use the EPA compounds in cases where a "systemic" treatment is indicated. While it is true that EPA seems to describe a preference for parenteral or enteral administration, one skilled in the art would not have overlooked that part of EPA which also teaches that the compounds may be administered

[9] In light of our discussion of why one skilled in the art would have made applicants' claimed composition, it is unnecessary to discuss applicants attack on the examiner's reliance on EPA's description of the ability of Compound A for treating lupus erythematosus. We view the examiner's reliance on lupus erythematosus, and applicants' attack thereon, to be a side show apart from the main event.

externally. Applicants, in effect, have attempting to limit the prior art to its preferred embodiments contrary to binding precedent. See e.g., (1) In re Burckel, 592 F.2d 1175, 1179, 201 USPQ 67, 70 (CCPA 1979) (a prior art disclosure is not limited to its preferred embodiments or specific working examples) and (2) In re Mills, 470 F.2d 649, 651, 176 USPQ 196, 198 (CCPA 1972) (CCPA found no merit in the argument that the disclosure of propylene is so submerged in the prior art reference, and the teaching of the use of ethylene so predominant, that the prior art reference cannot be said to place foams composed of the claimed ingredients in the possession of the public; all the disclosures in a reference must be evaluated, including nonpreferred embodiments, and a reference is not limited to the disclosure of specific working examples (citing In re Chapman, 357 F.2d 418, 424, 148 USPQ 711, 716 (CCPA 1966)).

According to applicants (Appeal Brief, page 6), EPA "does not disclose a single utility for the claimed compounds which can beneficially be treated locally". Applicants apparently have overlooked the fact that EPA teaches that its compounds have antimicrobial activity and the prior art has long applied antimicrobial compounds to skin ("external" to use EPA's word) in the form of lotions, gels and creams. Applicants' statement that the "cyclosporin art *** [is said to teach] that such compounds are generally not effective when administered in conventional topical forms" (Appeal Brief, pages 6-7), is at odds with EPA.

EPA itself teaches the "external" administration of its compounds which EPA says are antimicrobial agents.

3. New ground of rejection under § 112

Claims 19-22 and 24-26, but not claim 23, are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not contain an enabling description commensurate in scope with the breadth of the rejected claims.

We find, on this record, that a person having ordinary skill in the art would doubt that some compounds, having stereochemical configurations different from that of the compound mentioned in claim 23 and within the scope of the rejected claims, would be useful for topical administration to treat various pharmaceutical conditions. Applicants acknowledge in the specification, and repeat in their Appeal Brief, that the art supposedly recognizes that cyclosporins are not effective in typical topical administration. Accordingly, applicants express "surprise" with their finding that the claimed compounds are useful to topical administration.

The rejected claims cover not only the adequately disclosed isomer of claim 23, but other isomers. Insofar as we can tell, applicants' "surprise" is based on experimental work with isomers having the stereochemistry of the compound of claim 23. However, if one skilled in the art would not have expected the compounds of the rejected claims to be effective for topical administration, then one skilled in the art would reasonably question applicants' assertion that other isomers within the

scope of the rejected claims, other than the claim 23 isomer, would be effective for topical application. Applicants' discovery that a particular stereochemical configuration is effective, on this record, is not a convincing basis upon which to overcome a "doubt" which applicants say the prior art had with respect to cyclosporins generally. The application file contains no convincing evidence that, given applicants' success with one stereochemical isomer, one skilled in the art would have expected all or most of the stereochemical isomers of the rejected claims to have been suitable for topical administration.

To the extent that one might argue that our affirmance of the § 103(a) rejection is not consistent with our rejection based on § 112, we will observe that the description (actually inherent description) in EPA of the claim 23 isomer is the basis for our affirmance. We have not rejected claim 23 for lack of enablement.

C. Order

Upon consideration of the appeal, and for the reasons given, it is

ORDERED that the examiner's rejection based on EPA is vacated.

FURTHER ORDERED that all the claims on appeal are rejected as being unpatentable under 35 U.S.C. § 103(a) over (1) EPA, (2) Johnson, U.S. Patent 4,411,893 and (3) Showalter, U.S. Patent 4,556,654.

FURTHER ORDERED that all the claims on appeal, except for claim 23, are rejected under 35 U.S.C. § 112, first paragraph, as being based on a disclosure which would not enable a person having ordinary skill in the art to use the invention as broadly claimed.

FURTHER ORDERED that this opinion contains new grounds of rejection pursuant to Rule 196(b) (37 CFR § 1.196(b)).

FURTHER ORDERED that Rule 196(b) provides that, "A new ground of rejection shall not be considered final for purposes of judicial review."

FURTHER ORDERED that Rule 196(b) also provides that the applicant(s), **WITHIN TWO MONTHS FROM THE DATE OF ENTRY OF THIS DECISION**, must exercise one of the following two options with respect to the new ground of rejection to avoid termination of proceedings (§ 1.197(c)) as to the rejected claims:

> Option (1): Submit an appropriate amendment of the claims so rejected or a showing of facts relating to the claims so rejected, or both, and have the matter reconsidered by the examiner, in which event the application will be remanded to the examiner.
>
> Option (2): Request that the application be reheard under § 1.197(b) by

the Board of Patent Appeals and Interferences upon the same record.

FURTHER ORDERED that no time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

VACATED
(37 CFR § 1.196(b))

SHERMAN D. WINTERS
Administrative Patent Judge

WILLIAM F. SMITH
Administrative Patent Judge

FRED E. McKELVEY, Senior
Administrative Patent Judge

BOARD OF PATENT APPEALS AND INTERFERENCES

cc (via First Class mail):

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